

CLAIMS

1. Bispecific chimeric molecule comprising a domain capable of binding selectively a defined DNA sequence and a detecting domain capable of binding specifically a transactivator or a transrepressor or a transactivating or transrepressing complex characteristic of a physiological or physiopathological state.
2. Molecule according to claim 1, characterized in that the domain capable of binding selectively a defined DNA sequence is derived from a protein capable of interacting with the DNA.
3. Molecule according to claim 2, characterized in that the domain capable of binding selectively a defined DNA sequence is derived from a eukaryotic protein.
4. Molecule according to claim 3, characterized in that the domain capable of binding selectively a defined DNA sequence is derived from the proteins p53, STAT or NFkB.
5. Molecule according to claim 2, characterized in that the domain capable of binding selectively a defined DNA sequence is derived from a prokaryotic protein.
6. Molecule according to claim 5, characterized in that the prokaryotic protein is a bacterial repressor.
7. Molecule according to claim 6,

characterized in that the domain capable of binding selectively a defined DNA sequence is derived from the tetR protein.

8. Molecule according to claim 6,
5 characterized in that the domain capable of binding selectively a defined DNA sequence is derived from the Cro protein.

9. Molecule according to one of claims 2 to 8, characterized in that the domain capable of binding
10 selectively a defined DNA sequence comprises the domain for interacting with DNA of the said protein.

10. Molecule according to one of claims 2 to 8, characterized in that the domain capable of binding selectively a defined DNA sequence consists of a
15 complete protein.

11. Molecule according to claim 10, characterized in that the domain capable of binding selectively a defined DNA sequence consists of the tetR protein.

12. Molecule according to claim 10, characterized in that the domain capable of binding selectively a defined DNA sequence consists of the Cro protein.

13. Molecule according to claim 1,
25 characterized in that the domain capable of binding specifically the transactivator or transrepressor or the transactivating or transrepressing complex is an oligomerizing domain.

14. Molecule according to claim 13,
characterized in that the oligomerizing domain is a
leucine zipper, an SH3 or SH2 domain.

15. Molecule according to claim 13,
5 characterized in that the oligomerizing domain capable
of binding specifically the transactivator consists of
the C-terminal part of the p53 protein.

16. Molecule according to claim 15,
characterized in that the oligomerizing domain consists
of the C-terminal part of the p53 protein ranging from
residues 320 to 393 (SEQ ID No. 3), 302-360 or 302-390.

17. Molecule according to claim 1,
characterized in that the domain capable of binding
specifically the transactivator or transrepressor or
the transactivating or transrepressing complex is a
synthetic or natural domain known to interact with the
said transactivator or transrepressor or
transactivating or transrepressing complex.

18. Molecule according to claim 1,
characterized in that the domain capable of binding
specifically the transactivator or transrepressor or
the transactivating or transrepressing complex is an
antibody or an antibody fragment or derivative directed
against the transactivator or transrepressor or
transactivating or transrepressing complex.

~~19. Molecule according to claim 18,
characterized in that the domain capable of binding
specifically the transactivator or the transactivating~~

[illegible]

Complex consists of a Fab or F(ab)'2 fragment of antibodies or a VH or VL region of an antibody.

20. Molecule according to claim 18,
characterized in that the domain capable of binding
specifically the transactivator or the transactivating
5 complex consists of a single-chain antibody (ScFv)
comprising a VH region linked to a VL region by an arm.

21. Molecule according to claim 1,
characterized in that the DNA-binding domain and the
transactivator-binding domain are linked to each other
through an arm.

22. Molecule according to claim 21,
characterized in that the arm consists of a peptide
comprising 5 to 30 amino acids and, preferably, 5 to 20
amino acids.

23. Molecule according to claim 22, characterized in that the arm is chosen from the peptides of sequence SEQ ID No. 5 or SEQ ID No. 6.

24. Molecule according to one of the preceding claims, characterized in that the DNA-binding domain is situated at the N-terminal position and the transactivator-binding domain is situated at the C-terminal position.

25. Molecule according to one of claims 1 to 23, characterized in that the DNA-binding domain is situated at the C-terminal position and the transactivator-binding domain is situated at the N-terminal position.

[illegible]

26. Bispecific chimeric molecule of structure ScFv-VSV/myc-Hinge-TET or Cro (Figure 5A).

27. Bispecific chimeric molecule of structure ScFv-Hinge-TET or Cro (Figure 5B).

5 28. Bispecific chimeric molecule of
structure ScFv-TET or Cro (Figure 5C).

29. Bispecific chimeric molecule of structure TET or Cro-ScFv (Figure 5D).

30. Bispecific chimeric molecule of
10 structure TET or Cro-Hinge-ScFv (Figure 5E).

31. Bispecific chimeric molecule of structure Oligom-VSV/myc-Hinge-TET or Cro (Figure 5A), Oligom-Hinge-TET or Cro (Figure 5B) or Oligom-TET or Cro (Figure 5C).

15 32. Nucleic acid sequence encoding a
chimeric molecule according to ^{claim 1}~~one of claims 1 to 31.~~

~~33. Nucleic acid sequence according to claim~~
~~32, characterized in that it is a DNA sequence.~~

34. Nucleic acid sequence according to claim
20 32 or ~~33~~, characterized in that it is part of a vector.

35. Conditional system for the expression of genes comprising:

- a chimeric molecule as defined in ^{claim 1} ~~claims 1~~
to ~~31~~, and

25 - an expression cassette comprising a
regulatory sequence, a minimal transcriptional promoter
and the said gene.

~~36. Conditional system according to claim~~

35, characterized in that the DNA-binding domain of the chimeric molecule is represented by all or part of TetR and the regulatory sequence comprises the sequence SEQ ID No. 1 or a derivative thereof, optionally repeated several times.

37. Conditional system according to claim 35, characterized in that the DNA-binding domain of the chimeric molecule is represented by all or part of Cro and the regulatory sequence comprises the sequence SEQ ID No. 2 or a derivative thereof, optionally repeated several times.

38. Conditional system according to one of claims 35 to 37, characterized in that the minimal promoter comprises an INR or TATA box.

39. Conditional system according to claim 38, characterized in that the minimal promoter is derived from the promoter of the thymidine kinase gene.

40. Conditional system according to claim 39, characterized in that the minimal promoter is composed of nucleotides -37 to +19 of the promoter of the thymidine kinase gene.

41. Vector comprising:

- a nucleic acid sequence encoding a chimeric molecule according to one of ^{claim 1} ~~claims 1 to 31~~, and

- an expression cassette comprising a regulatory sequence, a minimal transcriptional promoter and a coding sequence of interest.

~~42. Vector according to claim 41,~~

characterized in that the minimal transcriptional promoter is defined according to claims 38 to 40.

43. Vector according to claim 41,
characterized in that the DNA-binding domain of the
5 chimeric molecule is represented by all or part of TetR
and the regulatory sequence comprises the sequence
SEQ ID No. 1 or a derivative thereof, optionally
repeated several times.

44. Vector according to claim 41,
10 characterized in that the DNA-binding domain of the
chimeric molecule is represented by all or part of Cro
and the regulatory sequence comprises the sequence
SEQ ID No. 2 or a derivative thereof, optionally
repeated several times.

15 45. Vector according to one of claims 41 to
44, characterized in that the coding sequence of
interest is a DNA sequence encoding a therapeutic
product.

46. Vector according to claim 45,
20 characterized in that the therapeutic product is a
toxic polypeptide or peptide.

47. Vector according to claim 46,
characterized in that the toxic therapeutic product is
chosen from diphtheria toxin, pseudomonas toxin,
ricin A, thymidine kinase, cytosine deaminase, protein
Grb3-3, or ScFv Y28.

48. Vector according to one of claims 41 to 47, characterized in that it is a plasmid vector.

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49. Vector according to one of claims 41 to 47, characterized in that it is a viral vector.

50. Vector according to claim 49, characterized in that it is a defective recombinant adenovirus.

51. Vector according to claim 49, characterized in that it is a defective recombinant retrovirus.

52. ~~Pharmaceutical composition comprising at least one vector according to one of claims 41 to 51.~~ *claim 41*

53. Nucleic acid comprising the sequence SEQ ID No. 4.

54. Molecule according to claim 1, characterized in that the transactivator characteristic of a physiological or physiopathological state is a protein of viral, parasitic, mycobacterial or cellular origin having a transcriptional transactivating activity.

55. Molecule according to claim 54, characterized in that the transactivator is a viral protein chosen from the HIV virus Tat protein, the papilloma virus E6/E7 proteins and the Epstein-Barr virus EBNA protein.

56. Molecule according to claim 54, characterized in that the transactivator is a cellular protein, preferably the mutated or wild-type p53 protein.

57. Molecule according to claim 1,

